IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

John R. Havens et al.

Serial No.: 09/410,368

Filed: September 30, 1999

For: BIOMOLECULAR ATTACHMENT SITES ON MICROELECTRONIC ARRAYS AND METHODS THEREOF

Group Art Unit: 1631

Examiner: Jerry Lin

DECLARATION OF MICHAEL HELLER, PH.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael Heller, Ph.D., do declare that:

1. I am a Professor in the Departments of Bioengineering and Electrical and Computer Engineering, at the University California, San Diego. I received a Ph.D. in Biochemistry from Colorado State University in 1973 and was an NIH Postdoctoral Fellow at Northwestern University from 1973-1976. I am a Co-Founder of Nanogen, Inc. and a consultant. I have a financial interest in Nanogen, Inc., assignee of the above-referenced application.

2. I have reviewed U.S. Application Serial No. 09/410,368 and the pending claims.

3. I have also reviewed U.S. Application Serial No. 10/170,172, Sosnowski et al. "Method for Enhancing the Hybridization Efficiency of Target Nucleic Acids Using a Self-Addressable, Self-Assembling Microelectronic Device," published as US 2003/0190632 A1, of which I am an inventor.

4. Example 3 of Sonsnowski uses a device in which the microlocations were fabricated from microcapillary tubes (0.2 mm x 5 mm) filled with 18-26% polyacrylamide containing 1% succinimidyl acrylate. (See paragraphs 0299 and 0304) The capillary tubes were mounted such that they shared a common upper buffer reservoir and had individual lower buffer reservoirs, each of which contained a platinum wire electrode. (See paragraph 0300) Each of the upper and lower buffer reservoirs were filled with 0.1 M sodium phosphate, pH 7.4. (See paragraph 0304) The capillaries were prerun for 10 minutes at 0.05 mA and then the capture sequence (ETIOAL) was added and electrophoretic transport was carried out for 2-5 minutes. (See paragraph 0304)

5. The 5'-amino terminus of the capture sequence reacted with the succinimidyl esters in the capillary tubes to form covalent bonds, thereby associating the capture sequence with a specific capillary.

6. The succinimidyl ester is very labile and reacts with primary amines without the need for any pH change to activate the succinimidyl ester. Any pH change would be incidental and would not be the cause of any chemical transformation that activates the succinimidyl ester.

7. Furthermore, Sosnowski does not teach that a pH change occurs in the overlying solution generated by providing an electrical potential at the electrode for the following reasons.

a) The experiment in Example 3 was performed at 0.05 mA in order to transport the capture sequence to a specific capillary tube. This current is too low to create a significant pH change in the buffer reservoir.

b) In the device used in Example 3, the top of the capillary tube and the shared common upper buffer reservoir are far removed from the platinum wire electrode located in the individual lower buffer reservoir. Therefore, any pH change that may

occur immediately around the electrode in the lower buffer reservoir would not cause any pH change in the capillary or in the upper buffer reservoir, which is where the reaction between the succinimidyl ester and the capture sequence occurs.

8. The reaction between the succinimidyl ester and the capture sequence occurs at relatively constant pH. Sosnowski mentions that the succinimidyl ester is "relatively labile, especially about pH 8.0." (Paragraph 0304, lines 7-8) Both high and low pH would cause the ester to hydrolyze, thereby rendering it useless (i.e., it can no longer react with the primary amine of the capture sequence). The presence of separate upper and lower buffer reservoirs ameliorates any potential change or fluctuation in pH with respect to the succinimidyl ester.

9. Therefore, the Sosnowski reference does not directly, or inherently, teach that the succinimidyl ester in the capillaries in Example 3 were activated by a chemical transformation caused by a pH change in an overlying solution generated by providing an electronic potential at an electrode before the ester reacts with the capture sequence.

10. I further declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent and application involved in the present proceedings.

Dated: Dec 8, 2006

Michael Heller, Ph.D.